IN THE CLAIMS:

1. A method to analyze gene expression comprised of:

providing a plurality of samples of biological material comprising an expression product of a gene sequence, arranged in a discrete compartment, wherein the plurality of samples contain gene expression products derived from at least two distinct biological conditions that may exhibit differential gene expression,

contacting each of the plurality of samples with an antibody wherein the antibody is specific to the expression product of a gene sequence, and

correlating the reaction between the antibody and the plurality of samples with expression of the gene sequence.

4. The method of claim 1 wherein the plurality of samples of biological material is comprised of samples from a human disease exhibiting differential gene expression.

7. The method of claim 1 further comprising the step of repeating the contacting step to identify a plurality of gene sequences associated with the biological condition.

Correction of Formalities

1. A new oath in compliance with 37 CFR 1.67(a) identifying the application by number and filing date is submitted herewith. The applicant has no known middle name or initial.

2. The specification is amended to specify the abbreviations referred to as "ab." in Figure 1 and "Idf." in Figure 2.

3. The alleged informality in the specification is not an informality in the context of the invention. The reference character "3" refers to a specific sample subtype that is used in comparison to another sample subtype. Whether or not the particular designation is as normal cells or samples derived from a normal patient is immaterial because the reference "3" may refer to any one of two samples in particular biological states. However, to facilitate progress of this application, the samples derived from a normal patient have been designated with the number 3, whereas the normal cells, as a subtype of the potential universe of samples from a normal patient, is designated as 3a in the specification. Similarly, because early stage cancer is a type of disease sample, the diseased samples are designated with the numeral 4, and an early stage cancer, as a subtype of the universe of potential diseased samples, is designated with the numeral 4a.

Claim Rejections – 35 USC § 112

The claim rejections detailed at paragraph 5 of the action are remedied as follows. The rejection of subparagraph a) is overcome by requiring that the biological conditions are those which may exhibit differential gene expression. Because the methodology of the invention is applicable to any two biological states, it is sufficiently definite to state that any two biological conditions having

the possibility of differential gene expression may be analyzed. The objection of subparagraph b) is eliminated by specifying that the biological material "comprises an expression product of a gene sequence." This language defines the fact that the biological material contains an expression product that may react with the plurality of antibodies in the method of the invention. In subparagraph c) the definition of human disease is rendered sufficiently definite by specifying that the human disease at issue in the methodology of the claim exhibits differential gene expression.

It should be noted that the method of the invention may be applied whether or not the specific disease exhibits known patterns of gene expression because, as is expressedly stated in the claim, the method of the invention is directed to analyzing gene expression such that in particular instances differences in gene expression may or may not exist for a particular disease.

Art-Based Rejections

None of claims 1-2, 4-6, or 11-13 are anticipated by Schlessinger et al. Schlessinger et al. does not disclose samples comprising of an expression product of a gene sequence oriented in discrete compartments wherein the samples exhibit differential gene expression. The only method for analysis disclosed by Schlessinger et al. and cited by the Examiner appears at column 17, wherein a method using a PYK2 nucleic acid probe is applied under hybridizing conditions. Therefore, the first element of claim 1 is not met by Schlessinger et al. and a rejection under 35 USC § 102(b) cannot stand. Furthermore, the correlation step of the present claims is not meaningfully disclosed in Schlessinger et al. The only section of Schlessinger et al. cited for the proposition that the correlation step is disclosed is lines 31-45 of column 22. That description relates to an antibody to a PYK2 polypeptide. Although Schlessinger et al. refers to analyzing PYK2 expression in tissue,

Schlessinger et al. does not disclose correlating any antibody/sample interaction with gene sequence expression. Moreover, given the remaining content of the pending claim, there is no indication that Schlessinger et al. contemplates correlating gene expression in distinct biological conditions to the PYK2 gene expression, that Schlessinger et al. analyze in other contexts, and Schlessinger et al. does not identify specific gene sequences from the expression analysis. Therefore, Schlessinger et al. cannot anticipate the pending claims 1-2, 4-6, and 11-13 under 35 USC § 102(b).

Claims 1 and 2 Are Not Anticipated by Margolis

The cited section of the Margolis patent is explicitly related to "identification of agents for treatment of oncogenic disorders." There is no reported attempt to analyze gene expression in any portion of the cited content of the Margolis patent. Even in the section of Margolis wherein an analysis of receptor PTK-adapter protein complex binding is analyzed, there is no analysis of gene expression conducted and no correlation between the binding reaction of Margolis and the gene expression characterized by two different biological conditions exhibiting differential gene expression. Thus, while Margolis coincidentally discloses protein binding reactions, there is no meaningful disclosure of a method for analyzing gene expression as in the current claims. Therefore, Margolis cannot anticipate pending claims 1 and 2 under 35 USC § 102(b).

35 USC § 103 – The Pending Claims Cannot be Rendered Obvious Under Section 103 of Title 35 Because a *Prima Facie* Case Cannot Exist Based on a Modification of the Cited References.

Referring to paragraph 11 of the office action, the application does not name multiple inventors and the provisions of 35 USC § 103 (c) and potential prior art under § 102(e), (f), or (g) does not exist.

On the merits of the § 103 issue, Applicant submits that neither of these references can be modified to establish a *prima facie* case against the claims of the present invention without engaging in a seriously flawed analysis under § 103. To establish a *prima facie* case under § 103, the Examiner must cite a reference that contains each element of the pending claims either through the combination of cited references or through the modification of a single reference. In this case, there is no combination of references and a *prima facia* case of obviousness based on a single reference cannot be established without an unwarranted modification of the claims, and, therefore, the claims are not obvious under § 103.

Two well established principles of the law of obviousness under 35 U.S.C. § 103 are "(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination" and "(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention," See MPEP § 2141, Basic Considerations Which Apply to Obviousness Rejections. Springing from these requirements are two other rules regarding the interpretation of prior art references: (1) as first explained in In re Gordon, 733 F.2d 900 (Fed. Cir. 1984), a prior art reference may not be modified in a way that would render the prior art invention unsatisfactory for its intended purpose (See MPEP § 2143.01), and (2) the portions of the prior art which teach away from the claimed invention must also be considered, W.L Gore & Assoc. Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983) (See MPEP § 2141.02). To reach the § 103 rejection, the cited references must both be modified to completely abandon their original purpose. There is absolutely nothing in the Schlessinger et al. reference, particularly at the section cited for contacting samples with an antibody (column 7, lines 42-46; column 17, lines 31-37; column 22, lines 31-32) that indicates that more than 100 antibodies should be raised in order to analyze the PYK peptides. There is absolutely nothing in Schlessinger et al.

that indicates that analyzing a number of antibodies is consistent with the invention of Schlessinger et al. which is directed to the use of the specific PYK peptides in various clinical and diagnostic embodiments. Since there is no indication that there are even 100 discrete antibodies that could be used to analyze the PKY polypeptide, the Examiner is suggesting that the reference be modified in a way that is completely contrary to the express purpose of Schlessinger et al. This is precisely the type of modification that is forbidden by the avoidance of hindsight analysis in the jurisprudence of 35 USC § 103.

A reconstruction and modification of Schlessinger et al. to yield a method using a reaction with 100 antibodies cannot be used to support an obviousness rejection without relying on impermissible hindsight unless a specific motivation exists in the prior art for one of ordinary skill to modify the particular elements of the invention in the claimed composition. As recently stated by the Court of Appeals for the Federal Circuit in In re Dembiczak:

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination"only by showing some objective teaching [leading to the combination]"); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). See also Graham, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not

with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, the Board fell into the hindsight trap.

The modifications proposed by the Examiner require the same hindsight analysis that was forbidden in the context of the combination of references under In Re Dembiczak. The desirability of reacting a number of samples with a large number of antibodies and correlating the results to gene expression is not even contemplated by the Schlessinger et al. et al. reference and no such modification would be made without knowledge gleaned from Applicant's invention and also departing from the purpose of Schlessinger et al. Such a modification would violate the rule explained in In re Gordon, 733 F.2d 900 (Fed. Cir. 1984) wherein the Federal Circuit held that a prior art reference may not be modified in a way that would render the prior art invention unsatisfactory for its intended purpose (See MPEP § 2143.01). Clearly, the raising of 100 antibodies to analyze the peptide of Schlessinger et al. for gene expression would render the art unsatisfactory for the intended purpose because there is no indication that 100 gene sequences are differentially expressed to yield the PKY peptide.

Furthermore, the present claims are not the recitation of an optimum or workable range for an invention where the general conditions of a claim are disclosed in the prior art. There is no disclosure in the prior art of a methodology that yields a sufficient number of antibodies, that can be directly correlated with gene sequence, such that an expression analysis of a large number of genes can be conducted by an antibody/gene product reaction. Under these circumstances, the applicant here is not merely discovering an optimal working range through the application of ordinary skill, but has discovered a new methodology that was not contemplated or enabled by the prior art. Under such circumstances, claim 3 is non-obvious under 35 USC § 103(a).

With respect to the Margolis reference, the Margolis reference is directed to the single example of detecting the expression of the PTK/adapter complex and the evaluation of disease disorders is explicitly stated to be an analysis for the presence or absence of the PTK/adapter protein complex depending on whether or not such a complex is normally present in a particular disorder. Margolis does not contemplate comparative gene expression analysis for a plurality of samples wherein a differential gene expression analysis for a number of sequences is determined by repeating an antibody binding reaction correlated to gene sequence expression. Because Margolis is not interested in developing a gene expression analysis for a particular biological condition, but rather is focusing on detection of the PTK/adapter complex, the method of the claims would be completely foreign to Margolis' method and Margolis does not contemplate any such methodology. As described above, when the § 103 requirement for a *prima facie* case is met by modifying a single reference, that modification must not depart from the intended purpose of the reference. In this case, Margolis has no legitimate purpose in repeating a contacting step that comprises contacting a plurality of samples with an antibody specific to the expression product of the gene sequence because Margolis would not secure any evaluation of a patient condition by that methodology. Thus, for the same reasons as with the Schlessinger et al. reference above, Margolis cannot be modified to meet the limitations of the method defined by the pending claims.

In light of the above, applicant requests favorable consideration and allowance of all of the newly presented claims. If the Examiner has any questions regarding the foregoing, or if the Examiner believes that an interview would facilitate the examination of this application, or if any additional information is required, the Examiner is invited to contact the undersigned at 949/567-2300, X 1124.

Respectfully submitted,

LYON & LYON LLP

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Kurt T. Mulville
Reg. No. 37,194

633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
(213) 489-1600